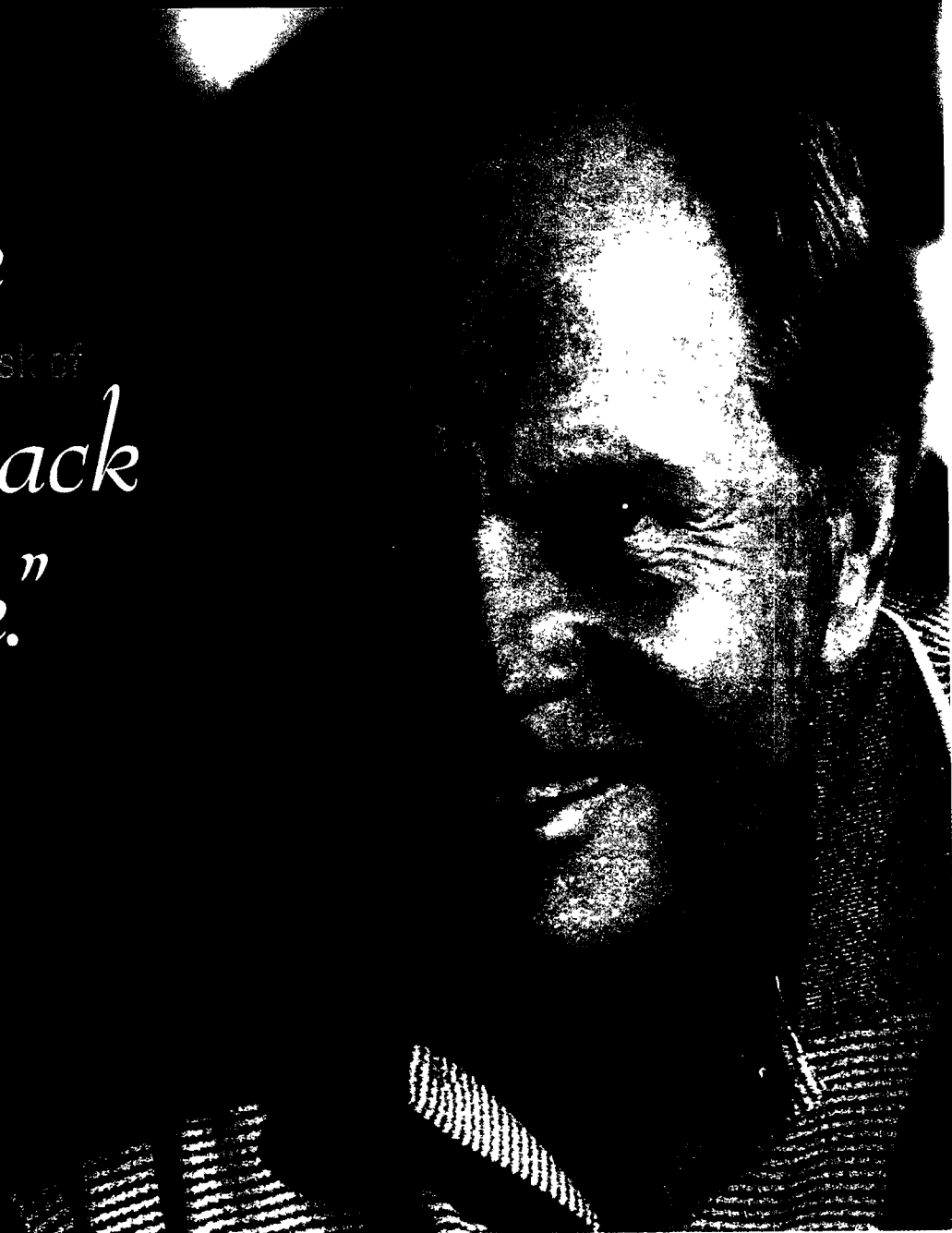


B

IF YOU'RE 55 OR OLDER AND HAVE HAD A HEART ATTACK OR STROKE, OR HAVE DIABETES PLUS ANOTHER CARDIOVASCULAR RISK FACTOR, SUCH AS SMOKING OR HIGH BLOOD PRESSURE...

*"Do more  
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or  
stroke."*

*"I take ALTACE for  
high blood pressure,  
but it may also help  
you in a different,  
important way."*



— Adding ALTACE to existing medications further reduces the risk of heart attack, stroke or cardiovascular death. —

Prescription ALTACE is not for everyone. ALTACE may cause swelling of the mouth, tongue, or throat, which could cause extremely serious risk and requires immediate medical care. Common side effects include persistent dry cough, dizziness, and light-headedness due to low blood

pressure. Do not take ALTACE during pregnancy, as death or injury to your unborn child may result, or if you've experienced serious side effects related to previous ACE inhibitors. Your results may vary. See adjacent page for important product information.



**You can do more**

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# ALTA<sup>®</sup> Capsules (ramipril)

## USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTA<sup>®</sup> should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal morbidity and mortality.

## CONTRAINDICATIONS

ALTA is contraindicated in patients who are hypersensitive to this product or any other angiotensin converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor)

## WARNINGS

**Anaphylactoid and Possibly Related Reactions: Angioedema** Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also CONTRAINDICATIONS.) Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTA should be discontinued and appropriate therapy instituted immediately. Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.5 ml to 0.5 ml) should be promptly administered. (See ADVERSE REACTIONS.)

**Anaphylactoid reactions during desensitization:** Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge. **Anaphylactoid reactions during membrane exposure:** Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption. **Hypotension** ALTA can cause symptomatic hypotension, after either the initial dose or a later dose when the disease has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTA. In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTA therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased. If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTA treatment usually can be continued following restoration of blood pressure and volume. **Hepatic Failure** Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up. **Neutropenia/Agranulocytosis** As with other ACE inhibitors, rarely, a mild - in isolated cases severe - reduction in the red blood cell count and hemoglobin content, white blood cell or platelet count may develop. In isolated cases, agranulocytosis, pancytopenia, and bone marrow depression may occur. Hematological reactions to ACE inhibitors are more likely to occur in patients with collagen vascular disease (e.g., systemic lupus erythematosus, scleroderma) and renal impairment.

Monitoring of white blood cell counts should be considered in patients with collagen vascular disease, especially if the disease is associated with impaired renal function. **Fetal/Neonatal Morbidity and Mortality** ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible. The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure. These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTA as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligohydramnios is observed, ALTA should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTA which crosses the placenta can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants. No teratogenic effects of ALTA were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 400 times (in rats and monkeys) and 2 times (in rabbits) the recommended human dose.

## PRECAUTIONS

**Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors,

including ALTA, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTA and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTA has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dose reduction of ALTA and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION.) **Hyperkalemia:** In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTA (ramipril). In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTA. (See DRUG INTERACTIONS.) **Cough:** Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. **Impaired Liver Function:** Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function. However, since the renin-angiotensin system may be activated in patients with severe liver cirrhosis and/or ascites, particular caution should be exercised in treating these patients. **Surgery/Anesthesia:** In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion. **Information for Patients Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible. **Angioedema:** Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTA should be discontinued until the physician has been consulted. All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia. **Drug Interactions With Nonsteroidal Anti-inflammatory agents:** Rarely, concomitant treatment with ACE inhibitors and nonsteroidal agents have been associated with worsening of renal failure and an increase in serum potassium. **With diuretics:** Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTA. The possibility of hypotensive effects with ALTA can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTA. If this is not possible, the starting dose should be reduced. (See DOSAGE AND ADMINISTRATION.) **With potassium supplements and potassium-sparing diuretics:** ALTA can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently. **With lithium:** Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased. **Other:** Neither ALTA nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The combination of ALTA and propranolol showed no adverse effects on dynamic parameters (blood pressure and heart rate). The co-administration of ALTA and warfarin did not adversely affect the anticoagulant effects of the latter drug. Additionally, co-administration of ALTA with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anti-coagulation. **Carcinogenesis, Mutagenesis, Impairment of Fertility** No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day. (For other species, these doses are about 200 times the maximum recommended human dose when compared on the basis of body surface area.) No mutagenic activity was detected in the Ames test in bacteria; the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility. **Pregnancy** Pregnancy Categories C (first trimester) and D (second and third trimesters). **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.** **Nursing Mothers** Ingestion of single 10 mg oral dose of ALTA resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving ALTA should not breast feed. **Geriatric Use** Of the total number of patients who received ramipril in US clinical studies of ALTA 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

**Hypertension** ALTA has been evaluated for safety in over 4,000 patients with hypertension, of these, 1,230 patients were studied in US controlled trials, and

1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTA and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTA in US placebo-controlled trials were headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTA patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTA. The most common reasons for discontinuation were cough (1.0%), "dizziness" (0.5%), and impotence (0.4%). Of observed side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials more than 1% of patients treated with ALTA, only asthenia (fatigue) was more common on ALTA than placebo (2% vs 1%). In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group, not attributed at that time to ramipril. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of patients requiring discontinuation of treatment. **Heart Failure Post Myocardial Infarction** Adverse reactions (except laboratory abnormalities) considered possibly/probably related to study drug that occurred in more than one percent of patients and more frequently on ramipril are listed below. The incidences representing experiences from the AIRE study (1004 ramipril patients, 982 placebo patients, follow-up time 6 to 46 months) include hypotension (ramipril 11%, placebo 5%), increased cough (ramipril 8%, placebo 5%), dizziness (ramipril 4%, placebo 3%), angina pectoris (ramipril 3%, placebo 2%), nausea (ramipril 2%, placebo 1%), postural hypotension (ramipril 2%, placebo 1%), syncope (ramipril 2%, placebo 1%), vomiting (ramipril 2%, placebo 0.5%), vertigo (ramipril 2%, placebo 0.7%), abnormal kidney function (ramipril 1%, placebo 0.5%) and diarrhea (ramipril 1%, placebo 0.4%). Safety data in the HOPE trial (4645 patients on ramipril and 4652 patients on placebo) were collected as reasons for discontinuation or temporary interruption of treatment. Discontinuation at any time occurred in 34% of patients on ramipril and 32% of patients on placebo. Permanent discontinuation occurred in 29% of patients on ramipril and 28% of patients on placebo. Reasons for stopping included cough (ramipril 7%, placebo 2%), hypotension or dizziness (ramipril 1.9%, placebo 1.5%), and angioedema (ramipril 0.3%, placebo 0.1%). The incidence of cough was similar to that seen in the AIRE trial. The rate of angioedema was the same as in previous clinical trials. (See WARNINGS.) Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarely events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain); events not likely to be drug related and minor events have been omitted. **Body As a Whole:** Anaphylactoid reactions. (See WARNINGS.) **Cardiovascular:** Symptomatic hypotension (reported in 0.5% of patients in US trials) (See WARNINGS and PRECAUTIONS); syncope and palpitations. **Hematologic:** Pancytopenia, hemolytic anemia and thrombocytopenia. **Renal:** Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTA, particularly when ALTA was given concomitantly with a diuretic. (See WARNINGS.) **Angioneurotic Edema:** Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.) **Gastrointestinal:** Pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, hepatitis, increased salivation and taste disturbance. **Dermatologic:** Apparent hypersensitivity reactions (manifested by urticaria, pruritus, or rash, with or without fever), erythema multiforme, pemphigus, photosensitivity, purpura, pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, and onycholysis. **Neurologic and Psychiatric:** Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances. **Miscellaneous:** As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/rheitis, myalgia, fever, vasculitis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations. Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported. **Fetal/Neonatal Morbidity and Mortality** See WARNINGS: Fetal/Neonatal Morbidity and Mortality. Other arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain. **Clinical Laboratory Test Findings: Creatinine and Blood Urea Nitrogen:** Increases in creatinine levels occurred in 1.2% of patients receiving ALTA alone, and in 1.5% of patients receiving ALTA and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTA alone and in 3% of patients receiving ALTA with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See WARNINGS and PRECAUTIONS.) Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See WARNINGS and PRECAUTIONS.) **Hemoglobin and Hematocrit:** Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTA alone and in 1.5% of patients receiving ALTA plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit. **Other (causal relationships unknown)** Clinically important changes in standard laboratory tests were rarely associated with ALTA administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities, all of these were cases of proteinuria or abnormal liver-function tests.

## OVERDOSAGE

Single oral doses in rats and mice of 10-11 g/kg resulted in significant lethality. In dogs, oral doses as high as 1 g/kg induced only mild gastrointestinal distress. Limited data on human overdosage are available. The most likely clinical manifestations would be symptoms attributable to hypotension. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

## Rx only

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